REMARKS

I. Status of Claims

Claims 1-99 were filed with the original application. Claims 90-99 were canceled and new claim 100 advanced in a preliminary amendment. Claims 5, 6 and 12-99 have been canceled. Thus, claims 1-4, 7-11 and 100 are under examination and are newly rejected under 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §103

Claims 1-4, 7-11 and 100 stand rejected as obvious over Dempsey in light of Wang, Matthews *et al.* and Metra *et al.* Applicants once again traverse.

A. Discussion of the Cited Art

At the outset, it is important to carefully review the teachings of each reference to understand what the person of skill in the art would have known, and understood, at the time of filing. In order to do this, the references will be addressed chronologically, as this best illustrates what the prior art landscape was.

The first paper in the chain of cited art was Matthews *et al.*, which was published in 1997. This paper clearly describes Bryostatin as an ***activator*** of protein kinase C (PKC) (page 20245, left hand column). It also clearly indicates that Bryostatin activates protein kinase D (PKD) through its activation of PKC, the latter kinase activating the former.

Second in the chain is Metra *et al.*, published in 1999. This paper is relatively unimportant to the overall rejection as it merely suggests that combining beta blockers with other cardiac drugs can be beneficial.

Third in the chain is Dempsey. In stark contrast to Matthews *et al.*, Dempsey describes Bryostatin as an inhibitor of PKC, ***but only under certain conditions***. Those limited conditions are spelled out quite clearly in the examples:

> The effect of bryostatin-1 on hypoxic growth and PKC isozyme expression in adult bovine pulmonary artery smooth muscle cells was tested. Hypoxic growth was induced by priming with the PKC activator, 10 nM PMA. Proliferative response was measured by ^{3}H-thymidine incorporation and cell counts. Isozyme expression was measured by Western blot. Pretreatment with 10 to 100 nM bryostatin-1 for 4 or 24 hr inhibited the proliferative response to PMA and hypoxia (3% oxygen). Inhibitors of the Ca^{2+}-dependent isozymes of PKC (1.0 μM GF1092203X and Go6976) had similar anti-proliferative effects. This data suggested that bryostatin-1 might be down-regulating one or more of the Ca^{2+}-dependent isozymes in pulmonary artery smooth muscle cells. Therefore, the differential effects of bryostatin-1 on PKC isozyme expression were determined. bryostatin-1 (100 nM) rapidly induced the proteolytic degradation of PKC-α in smooth muscle cells, with degradation first detectable by 1 hour and complete by 24 hours. The threshold concentration to induce degradation was 10 nM, with a maximal effect at 50 to 100 nM. This same amount of bryostatin had been found to inhibit hypoxic growth. The down-regulating effect of bryostatin-1 was isozyme-selective. No degradation of the other Ca^{2+}-dependent isozyme expressed in these adult cells (βI) or five other Ca^{2+}-independent isozymes was detected (δ,ε,ς,ι,μ). These results suggest that bryostatin-1 inhibits hypoxic growth of PA SMC by a mechanism that is dependent on PKC-α and may be useful in attenuating abnormal smooth muscle cell growth both *in vitro* and *in vivo*. See L. J. Ruff and E. C. Dempsey, "BRYOSTATIN-1 ATTENUATES HYPOXIC GROWTH OF BOVINE PULMONARY ARTERY SMOOTH MUSCLE CELLS IN VITRO," FASEB J 12:A339, 1998.

Dempsey, columns 12-13. Thus, as is readily seen, these data show that only at ***higher*** concentrations of Bryostatin and other PKC activators does one see the PKC inhibition. Moreover, this experiment used ***pretreatment of cells*** with Bryostatin at 10-100 nM or GF1092203X and Go6976 at even higher levels (1.0 μM), and thus can say nothing about the ability to ***reverse*** existing activation of PKC, and hence PKD.

The other experiment was performed as follows.

> Bryostatin-1 was tested in a murine model of chronic hypoxic PHTN. Adult ICR mice were exposed to normoxia (N) (5,200 ft, Denver altitude) or hypoxia (H) (18,000 ft) for 4 weeks and received either no treatment (n=15-20), vehicle (DMSO; n=8), or bryostatin-1 at 11 or 33 μg/kg/d (n=13 and 7-10, respectively), delivered intraperitoneally. Hematocrit (Hct [%]), RV/LV+S, and RV systolic pressure (RVSP [mmHg]) were measured under normoxic conditions at 0 or 48 hr following removal from chamber. The results are shown in Table I. Chronic hypoxia caused an increase in Hct which was unchanged by vehicle or bryostatin-1. Hypoxia induced a rise in RV/LV+S and in RVSP. Initial (0 hour) measurements of RVSP following hypoxia in vehicle and drug treated groups were not different. However, when the measurements were made 48 hours later, an attenuating effect of bryostatin-1 on the hypoxia-induced increase in RVSP was detected. In conclusion, bryostatin-1 had attenuating effects in an adult murine model of chronic hypoxic pulmonary hypertension and is believed to be a useful pharmacological tool for the treatment this important clinical problem.

Dempsey, columns 13-14. A careful review of Table 1 shows that the results do not support Dempsey's conclusions. RSVP in normal mice treated with the vehicle was 31 ± 3 mmHg at t = 48 hrs, as compared with hypoxic mice at 40 ± 2 mmHg. For the Bryostatin-treated animals, the numbers were 30 ± 2 mmHg (normal animals) and 34 ± 2 mmHg (hypoxic). Thus, taking the error bars at their least favorable, the treatment might have resulted in absolute values of 28 mmHg for normal versus 36 mmHg for treatment, roughly the average difference in untreated animals. This is hardly convincing evidence of efficacy. Notably, no *in vivo* data with either of the true PKC-inhibitors GF1092203X and Go6976 were provided.

Finally, the article from Wang in 2006 is ***not*** prior art against the present claims and should not be considered when formulating an ***obviousness*** rejection (the prior reliance on Wang in the context of an anticipation rejection was not challenged). Regardless, Wang merely provides the mechanistic aspect of phosphorylation of PKD by PKC, which is not reflected in the current claims.

B. The Present Claims

The claims have been amended to more clearly recite both the nature of the pathology to be treated, and the effects provided by the treatment. Thus, claim 1 now recites:

> 1. A method of inhibiting pathologic cardiac hypertrophy and hypertension in a human patient comprising:
>
> (a) identifying a human patient having cardiac hypertrophy and hypertension;
> (b) administering to said patient an inhibitor of Protein Kinase D (PKD); and
> (c) administering to said patient a beta blocker,
>
> wherein said PKD inhibitor reduces hypertrophic signaling and inhibits hypertrophy in cardiac tissue of said human patient, and said beta blocker reduces hypertension in said human patient.

As is immediately evident, present claim 1 requires treatment of both hypertrophy and hypertension, and further calls out the ability of a PKD inhibitor to reduce hypertrophic signaling in cardiac tissue, thereby inhbiting hypertrophy itself, and not merely some symptom thereof.

C. Rebuttal of the Rejection

Applicants submit that the rejection is improper because it makes a number of unwarranted assumptions regarding what those of skill in the art would have believed based on the cited art at the time of filing. And, as will be explained, there is no evidence that PKC inhibitors could or should be used at physiologically relevant concentrations to treat cardiac hypertrophy.

Bryostatin. As already explained above, the bulk of the data from Dempsey deals with Bryostatin. No matter how that molecule might be characterized in Dempsey, ***it is not a PKC or PKD inhibitor***. Going back far earlier than Matthews *et al.*, *i.e.*, to 1985, and continuing up to today (as evidenced by the Wikipedia entry for Bryostatin; attached), this drug is characterized

as a ***PKC activator***. As such, even if one were to accept Dempsey's ***conditional*** classification of Bryostatin as a high dose PKC inhibitor, one would ***not*** seek to use it as an inhibitor of PKD, or for the treatment of cardiac hypertrophy, simply because of its ability to ***activate*** PKC at lower levels. Moreover, the fact that it might have inherently inhibited PKD at higher concentrations is not a fact that the skilled artisan could consider when assessing obviousness of its use in the claimed invention.

Go6976 and GF1092203X. Dempsey provides evidence in a flawed *in vitro* molecule suggesting that two PKC inhibitors also work to block pulmonary artery smooth muscle proliferation. However, the concentrations tested were non-physiologic (1 μM) and would hardly convince the skilled artisan to use these compounds to inhibit cardiac hypertrophy, even if they ***might*** be useful in inhibiting hypertension. Moreover, the extremely shaky *in vivo* data provided by Dempsey failed to include any information on these two compounds, or any other true PKC inhibitors. Finally, there would be no reason to equate data from Bryostatin with Go6976 and GF1092203X for the simple reason that the latter two do not activate PKC at any concentration.

Hypertrophy. The claims as presented for reconsideration now recite very specific therapeutic parameters that are not found either explicitly or inherently in the references as cited. First, it is now required that the PKD inhibitor reduce hypertrophic signaling and hence inhibit hypertrophy, and that the beta blocker inhibit hypertension. There is no evidence to suggest that Bryostatin had any actual effect on hypertrophic signaling in Dempsey's studies. Moreover, there is nothing in Dempsey's work to suggest that true PKC inhibitors would be useful in treating cardiac hypertrophy.

Inherency. The examiner's continued reliance on Wang suggests that inherency is still playing a role in this rejection. While the courts have, at times, suggested than inherency can be properly applied in the context of obviousness rejections, by nature that rule must be applied with a great deal of circumspection. This is true for the simple reason that obviousness requires an analysis of what the skilled artisan would believe is suggested by the art, and things which are inherent cannot influence the thinking of the skilled artisan.

Here, the examiner will no doubt say that because PKC inhibition was suggested for treating a ***symptom*** of cardiac hypertrophy, the presumed unrecognized benefit of reduced hypertrophic signaling would be an inherent additional benefit. However, the claims as presented for reconsideration do not simply posit treating a symptom of hypertrophy, they posit treatment of hypertrophy itself. This feature is clearly lacking from the art, and thus the skilled artisan, when presented with ***that*** goal, would not have turned to either Bryostatin or a true PKC inhibitor, for the reasons set forth above.

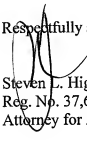
D. Summary

In sum, what is presented by the examiner here is the vestiges of a failed inherency rejection that simply do not work in the context of obviousness, and certainly not when considered in light of the claims as presented for reconsideration. Thus, again, it is submitted that there is insufficient evidence from Dempsey that one should use a true PKC inhibitor in any method, much less that doing so would have an impact on cardiac hypertrophy (as opposed to some symptom thereof) through inhibition of PKD function. Given these deficiencies, a *prima facie* case of obviousness will not stand. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this submission, a telephone call to the undersigned is invited.

Respectfully submitted,



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